

which maintains immunogenicity, wherein said polynucleotide sequence comprises at least one codon optimized for expression in a human host.

REMARKS

The Official Action mailed June 5, 2002, and the references cited therein have been carefully considered. Reconsideration of this application as amended is respectfully requested in light of the foregoing amendments and following remarks.

Claims 1-30 are pending and have been rejected. Claims 5, 8, 12 and 16 have been cancelled without prejudice. Claims 1, 6, 9, 10, 13, 14, 17, 19, 21-26, 28 and 30 have been amended. Support for the amendment to claims 1 and 30 can be found on page 1, lines 16-20 and page 8, lines 13-17.

Claim Rejections Under 35 U.S.C. §112

1. Claim Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-30 have been rejected under 35 U.S.C. §112, first paragraph as containing subject matter that has not been adequately described in the specification to convey to one skilled in the art that the inventors had possession of the invention. In essence, the view put forth in the Office Action is that the claimed genus is overly broad in view of the representative species described, wherein said species are alleged to lack 1) sequences or characteristics that can be attributed to all possible or representative alternate codons desirable for expression in human cells, 2) the identifying characteristics of such alternate codons, and 3) the structure-function relationship of the alternative codons. As such, it is alleged that the Specification does not provide a reasonable guide for those skilled in the art to practice the invention. Applicants respectfully traverse this rejection in view of the nature of the invention and the description provided.

An adequate written description of claims drawn to a genus may be satisfied through a sufficient description of a representative number of species. Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112 (1) Written Description Requirement, 66 Fed. Reg. 1099, 1106 (2001) (hereinafter “Guidelines”). While satisfaction of a “representative number” depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes of the elements possessed by the members of the genus in view of the species disclosed, the description of a single species may adequately support a genus. Guidelines at 1106. The description in a specification does not need to rise to the level to be of such specificity that it would provide individual support for each

species that the genus embraces. Id. The Guidelines further specify that what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Id. Because the specification is directed to one of skill in the art, the absence of definitions or details for well established terms or procedures should not be the basis of a rejection under 35 U.S.C. §112 (1) for lack of written description. Guidelines at 1105. It is axiomatic that information which is well known in the art need not be described in detail in the specification. Id., citing Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1379-80, 231 USPQ 81, 890 (Fed. Cir. 1986).

The instant invention is directed to synthetic DNA molecules that encode HPV proteins, wherein "synthetic" has been defined as HPV genes which have been modified so that they contain codons which are preferred for human expression (see Specification at page 6, lines 22-25). Contrary to the assertions made in the Office Action, the invention claimed does not encompass all possible alternate codons for a broad class of proteins. Rather, the invention is directed to a sub-set of nucleotide sequences that encode codons that would facilitate the expression of HPV proteins in a human host cell. Applicants have provided numerous examples directed to four proteins and three HPV serotypes (Examples 1-8) and have provided a description of the specific changes that were utilized to create mutants thereof (see page 8, lines 13-27) to facilitate expression in a human host cell. Given the nature of molecular biology, the level of skill in the art is inherently high. As such, the illustration of the invention with the given examples in the Specification is more than adequate to demonstrate that Applicants were in possession of the claimed invention.

Moreover, the ability to select and modify specific codons that would facilitate expression in a human host cell is well within the abilities of those of ordinary skill in the art given not only the description provided by the Applicants, but based on the knowledge available in the prior art. Applicants provided a description, starting at page 7, line 15, in the Specification, which is based on a publication more than fifteen years prior to the filing of this application, of the methodology needed to carry out codon optimization (Lathe et al., *J. Mol. Biol.* 183:1-12 (1985) (a copy of which is enclosed with this response)). Lathe describes in detail a statistical method for designing oligonucleotides with improved homology with a given target. The reference also describes the most frequent (or optimal in the cases of R and S) codon for each amino acid and the expected frequency of utilization within the human genome. Lathe, at page 5, Col. 2, paragraph 3. Using this data, it would be well within the abilities of those skilled in the art of molecular biology to design nucleotide sequences in which the codons have been optimized for human expression. In addition, Applicants submit herewith two references

that demonstrate that those skilled in the art would have been able to choose specific codons for modification and the means to optimize their use for human expression of HPV. See, Zhou, J. *et al.*, J. of Virology, Vol. 73, No. 6, 4972-4982 (1999) (copy previously provided as reference of Applicants' IDS). See, in particular, the paragraph that bridges pages 4972-4973 in which they describe substituting codons used by mammalian genes for codons used in the original bovine sequence. As further demonstrated by Liu, W. J. *et al.*, Vaccine, 20: 862-869 (2002), at p. 863, Col. 1, Sec. 2.2 (a copy of which is enclosed with this response), the technique of codon optimization is a matter of routine skill in the art. Thus, those skilled in the art would reasonably believe that Applicants had possession of the instant invention that has as an element a codon-optimized sequence.

Notwithstanding and to advance prosecution of this application, Applicants have amended the claims to direct the scope of the invention claimed to HPV serotype 16. Thus, the number of examples, along with the description and sequences provided, are more than adequate to satisfy the written description requirement.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 1-30 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement with respect to use of the claimed invention as a vaccine for humans. More specifically the Office Action alleges that while the Specification is enabling for inducing an immune response in mice, it does not reasonably provide enablement to those skilled in the art for inducing a protective immune response to HPV in humans using the claimed invention. Applicants respectfully traverse this rejection. Notwithstanding and to advance prosecution of the present application, Applicants have amended the pending claims to more distinctly claim a synthetic polynucleotide encoding a codon-optimized HPV16 protein or a mutant thereof.

To satisfy the enablement requirement of U.S.C. §112, first paragraph, all that is necessary is that one skilled in the art be able to practice the claimed invention. The scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See for example, In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The training materials prepared by the USPTO for its examiners further elaborate that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." Even if the examiner believes that there is contradicting evidence, the examiner must weigh the evidence for and against and make a determination as to whether one skilled in the art would accept the model as reasonably correlating to the condition. Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical

Applications (hereinafter "Training Materials"), A.2.c.ii, page 11, citing *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). The Training Materials further state that it is not necessary that there be a complete correlation or that statistical results be obtained; a rigorous or an invariable exact correlation is not required. *Id.* Example 5E of the Training Materials makes it clear that method of treatment claims are enabled to the degree necessary to satisfy the §112, first paragraph requirement, when animal studies accepted by those of skill in the art as reasonably correlative with treatment in other mammals have been conducted.

Applicants are claiming a method of inducing an immune response to an HPV infection. It is generally accepted by those skilled in the art that the immune system is important in the control of HPV infections, see *zur Hausen, H.*, *Nature Reviews Cancer*, Vol. 2, 342-350 (2002), p. 345, Col. 1-2 (a copy of which is enclosed with this response). Because of the malignancies induced by HPV, surrogates for human hosts are needed to evaluate vaccines to this disease, *Id.* at p.347, Col. 1. Those skilled in the art of HPV vaccine development clearly recognize and accept that based on animal studies, that human vaccines are expected to be effective. *Id.* at p. 347, Col. 2. *Zur Hausen* summarizes the studies that have been undertaken and their importance for vaccine development. *Id.* In the instant application Applicants have utilized a mouse that is expressing a human gene to evaluate the effectiveness of the claimed composition for inducing an immune response in a human. Applicants submit herewith three references as examples that demonstrate that those skilled in the art would have a reasonable expectation of success based on animal studies that an immune response could be induced in a human and that this approach has been generally accepted by those skilled in the art for investigation of HPV vaccines. See *Chen, L. et al.*, *Proc. Natl. Acad. Sci. USA*, Vol 88, 110-114 (1991); *Feltkamp, M. et al.*, *Eur. J. Immunol.* 23, 2242-2249; and *Lin, K. et al.*, *Cancer Research* 56, 21-26 (1996) (copies of which are enclosed with this response). More importantly, the very art which the Examiner cites as anticipatory under 35 U.S.C. §102, utilizes such an approach (Ertl *et al.*, U.S. Pat. No. 6,019978 and suggests that DNA vaccines merit consideration for use in humans (Donnelly *et al.*, *J. Infect. Dis.* 713, 314-320 (1996)) based on the animal studies conducted therein. The Office Action admits that Ertl teaches an adenoviral vector that expresses an HPV protein could be used to induce a protective immune response (claims 1-6). As such, Applicants use of a mouse host that is expressing a human gene is not only generally accepted by those skilled in the art, it is the most prudent means to evaluate the effectiveness of this type of vaccine.

The Office Action also alleges that the large number of species, i.e any protein having an alternative codon, encompassed by the claims are not enabled by the Specification. As

pointed out above, Applicants are not claiming "any protein having an alternative codon", but rather sequences that have been codon-optimized for the expression of a human HPV16 protein. This is not an unlimited set of proteins. Given the high level of skill in the art, the examples provided, along with the description of codon-optimization in the prior art, those skilled in the art would be able to make and use the claimed invention. With respect to the claimed mutants, those skilled in the art of HPV vaccines understand that the reference to "reduced protein function" with respect to mutants as compared to the wild type proteins, refers to the mutants reduced ability to carry out viral replication and cellular transformation associated with the specific genes in question. See Specification at page 1, lines 17-20, and page 8, lines 13-17. Applicants have amended the claims to further clarify that the "reduced protein function" refers specifically to this aspect.

Further the comparison of the claimed invention to gene therapy appears to be misplaced. The claimed invention is not directed to a method in which new genetic material is being introduced to the host for the purposes of augmenting or replacing the host's genome. See, Kahl, G., The Dictionary of Gene Technology, Second Edition, Wiley-VCH , page 767 (2001) (a copy of which is enclosed with this response). On the contrary the invention is directed to a method of inducing a biological response, i.e. an immune response, wherein said response is evoked by the protein expressed. Similarly, the claimed invention is not directed to a vaccine for cancer. Rather, as the zur Hausen reference clarifies, an HPV infection results in a cascade of events, the ultimate one of which is the development of a cancer. See, zur Hausen at pp. 343-344. The claimed invention is directed to prevention of the triggering event, i.e. the infection by HPV, not the formation of cancer once the host has been infected with HPV. As zur Hausen further sets forth, the development of vaccines for HPV has been shown to have important consequences for cancer prevention. zur Hausen, p. 347, Col. 2. Thus, the rejection based on the belief that the instant invention is not enabled for cancer immunotherapy (which is generally regarded to be a therapy intended to directly attack the malignancy, see, for example, Craig, C. and Stitzel, R., Modern Pharmacology, Little, Brown and Company (1994) , page 666 (a copy of which is enclosed herewith) appears to be misplaced. Applicants have provided sufficient description for those skilled in the art of HPV vaccines to use the claimed composition for the purpose of inducing an immune response in a human. As such, the accepted *in vitro* and animal studies utilized herein are sufficient to satisfy the enablement requirement of §112, first paragraph.

In view of the above, it is respectfully requested that this rejection be withdrawn.

2 Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1 and 30 have been rejected as being indefinite with respect to the phrase "reduced protein function". Applicants have amended these claims as noted above to more distinctly claim the invention.

Claims 24-30 have been rejected as being indefinite with respect to the steps of the claimed method for inducing an immune response. It is respectfully noted that claim 30 is directed to a method of making the claimed composition, not a method of use. It is assumed for purposes of this response that the Examiner intended this rejection to encompass claims 24-29. Notwithstanding and to advance prosecution, Applicants have amended the claims to clarify that the claimed composition is to be administered to a vertebrate in the manner claimed. Those skilled in the art would understand the routine steps by which a composition of this nature could be administered, i.e subcutaneous or parenteral based on the description provided in the Specification (Specification beginning at page 11, line 22, through page 12, line13).

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claim Rejections Under 35 U.S.C. §102

1. Rejection in View of Hofmann *et al.* (U.S. Pat. No. 6,159,729)

Claims 1-6, 22 and 30 have been rejected under 35 U.S.C. §102(e) in view of Hofmann. It is alleged that said reference anticipates the claimed invention in that it teaches the use of sequences encoding a HPV protein, which can be selected from different serotypes including HPV 11 and 16. Applicants respectfully traverse this rejection. It should be noted that claim 5 has been cancelled and, as such, the rejection is moot as to this claim. Claims 1, 22 and 30 have been amended to further clarify that the claimed invention is directed to a nucleotide sequence that encodes a codon-optimized HPV16 protein. As to the instant reference, in that the sequences utilized therein were used for expression in yeast (Example 6), nor does it teach the use of a codon-optimized sequence, it cannot anticipate the claimed invention directed to a HPV16 oligonucleotide sequence that has been codon-optimized for expression in a human host cell.

2. Rejection in View of Joyce *et al.* (U.S. Pat. No. 5,820,870)

Claims 1-5, 22 and 30 have been rejected under 35 U.S.C. §102(e) in view of Joyce.

It is alleged that the reference anticipates the claimed invention in that it teaches the use of a human HPV18 L1 and L2 protein in an expression vector for the use of expression in

a host cell. Applicants respectfully traverse this rejection. It should be noted that claim 5 has been cancelled and, as such, the rejection is moot as to this claim. Claims 1, 22 and 30 have been amended to further clarify that the claimed invention is directed to a nucleotide sequence that encodes a codon-optimized HPV16 protein. As to the instant reference, in that the sequences utilized therein were used for expression in a yeast host cell (Example 13), nor does it teach the use of a codon-optimized sequence, it cannot anticipate the claimed invention directed to a HPV16 oligonucleotide sequence that has been codon-optimized for expression in a human host cell.

3. Rejection in View of Whittle *et al.* (U.S. Pat. No. 6,123,948)

Claims 1-6, 8-10, 12, 13, 16, 17, 22 and 30 have been rejected under 35 U.S.C. §102(e) in view of Whittle. It is alleged that the reference anticipates the claimed invention in that it teaches a fusion protein of HPV6 L2 and E7. Applicants respectfully traverse this rejection. It should be noted that claims 5, 8 and 16 have been cancelled and, as such, the rejection is moot as to these claims. Claims 1, 22 and 30 have been amended to further clarify that the claimed invention is directed to a nucleotide sequence that encodes a codon-optimized HPV16 protein. As to the instant reference, in that the sequences utilized therein were used for expression in a yeast host cell (Examples 9-11), nor does it teach the use of a codon-optimized sequence, it cannot anticipate the claimed invention directed to a HPV16 oligonucleotide sequence that has been codon-optimized for expression in a human host cell.

4. Rejection in View of Ertl *et al.* (U.S. Pat. No. 6,019,978)

Claims 1-6, 19, 20, 21 and 26 have been rejected under 35 U.S.C. §102(e) in view of Ertl. It is alleged that the reference anticipates the claimed invention in that it teaches an adenoviral vector having a deletion in the E1 region and an insert in the E1 region, wherein the insert comprises a polynucleotide encoding a HPV protein, its use for inducing a protective immune response. Applicants respectfully traverse this rejection. It should be noted that claim 5 has been cancelled and, as such, the rejection is moot as to these claims. Claims 1, 21 and 26 have been amended to further clarify that the claimed invention is directed to a nucleotide sequence that encodes a codon-optimized HPV16 protein. As to the instant reference, in that the sequences disclosed therein were used for expression in a yeast host cell (Examples 9-11), nor does it teach the use of a codon-optimized sequence, it cannot anticipate the claimed invention directed to a HPV16 oligonucleotide sequence that has been codon-optimized for expression in a human host cell.

In view of the above, it is respectfully requested that these rejections be withdrawn.

Claim Rejection Under 35 U.S.C. §103

Claims 1-6, 8-10, 12, 13, 16, 17, 19-26, 28 and 30 have been rejected under 35 U.S.C. §103 as being unpatentable over Ertl (claims 1-6, 19, 20, 21 and 26) and Whittle (claims 1-6, 8-10, 12, 13, 16, 17, 22 and 30) and further in view of Donnelly *et al.* (J. Infect. Dis. 713, 314-20 (1996)). Applicants respectfully traverse this rejection. It should be noted that claims 5, 8, 12 and 16 have been cancelled and, as such, the rejection is moot as to these claims. Claims 1, 19, 21, 22, 26 and 30 have been amended to further clarify that the claimed invention is directed to a nucleotide sequence that encodes a codon-optimized HPV16 protein.

According to the argument used to support this rejection, there was motivation to combine these references to arrive at the claimed invention because:

(1) Ertl teaches an adenoviral vector comprising a deletion in the E1 region and which can be used to induce a protective immune response against HPV (claims 1-6) in mice. It is admitted that Ertl does not teach immunization with a plasmid vector encoding HPV proteins or a V1Jns plasmid.

(2) Whittle teaches a polynucleotide sequence encoding a fusion protein HPV6 L2 and E7 in an expression vector. The antigenic determinants for the fusion protein could be selected from different serotypes of HPV. It is admitted that Whittle does not teach nucleic acid immunizations.

(3) Donnelly teaches a polynucleotide sequence encoding a rabbit papillomavirus (CRPV11) protein (L1 and L2) in an expression vector (V1Jns). It is admitted that the results suggest that DNA vaccines merit consideration as a potential alternative for the vaccination of humans against HPV.

As to the instant rejection, notwithstanding that there is no motivation provided by the references cited to combine their teachings, the combined references do not disclose or teach all the elements of the claimed invention. As discussed above, the sequences utilized in Ertl were used for expression in a yeast host cell; none of the cited references teach the use of a codon-optimized sequence. As such, the cited combination of references cannot render the claimed invention obvious as they do not disclose all of the elements of the claimed invention.

In view of the above, it is respectfully requested that this rejection be withdrawn.

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CONDITIONAL PETITION

Applicant hereby makes a Conditional Petition for any relief available to correct any defect in connection with this filing, or any defect remaining in this application after this filing. The Commissioner is authorized to charge deposit account 13-2755 for the petition fee and any other fee(s) required to effect this Conditional Petition.

CONCLUSION

In view of the foregoing amendments and remarks, it is seen that the grounds of rejections have been overcome and that Claims 1-4, 6, 7, 9-11, 13-15 and 17-30 are in proper condition for allowance. Accordingly, Applicant respectfully requests that all of the rejections of record be withdrawn and a Notice of Allowance be forwarded to the Applicant. The Examiner is invited to contact Applicant's Attorney at the telephone number given below, if such would expedite the allowance of this application. Favorable action is earnestly solicited.

Respectfully submitted,

By 

Joan E. Switzer
Reg. No. 34,740
Attorney for Applicant

MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-5616

Date:

10/7/02